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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,678	08/05/2003	Chih-Hung Lee	6888.US.P1	7170

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EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/634,678	LEE ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/20/2004 (IDS)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-97* is/are pending in the application.

4a) Of the above claim(s) *2-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 77-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. §1.67(a) identifying this application by its Serial Number and filing date is required. See MPEP 602.01 and 602.02. The oath or declaration is defective because:

It does not include signatures for all but one of the listed inventors.

The Abstract of the Disclosure is objected to because is does not meet the requirement of the MPEP for US application. Correction is required. See MPEP 608.01(b).

The Abstract of the Disclosure is objected to because the variables required to define the chemical compounds being referred to in the abstract have not been defined in the abstract. Correction is required. See MPEP 608.01(b).

Claims **1-84** remain in the case.

No claims have been cancelled, no claims have been amended, the disclosure has not been amended, and no preliminary amendments have been filed as of the date of the instant Office action. One Information Disclosure Statements (IDS) filed February 25, 2004 has been received with all cited references and made of record.

Claims **1-97** remain in the case.

Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claims **2-59 and 64-67**, drawn to 5-substituted **isoquinolines**, pharmaceutical compositions thereof, and methods of medicinal treatment by administration thereof, classified in Class 514, subclass 307.000 and Class 546, subclass 143.000.

II. Claims **60-63**, drawn to substituted **cinnolines**, pharmaceutical compositions thereof, and methods of medicinal treatment by administration thereof, classified in Class 514, subclass 247.000 and Class 544, subclass 235.000

III. Claims **68-76**, drawn to 5-substituted **indoles**, pharmaceutical compositions thereof, and methods of medicinal treatment by administration thereof, classified in Class 514, subclass 415 and Class 548, subclass 409.000.

IV. Claims **77-93**, drawn to substituted **indazoles**, pharmaceutical compositions thereof, and methods of medicinal treatment by administration thereof, classified in Class 514, subclass 406.000 and Class 548, subclass 361.100.

Claims **1 and 94-97** link inventions **I, II, III and IV** and will be examined with the elected invention to the extent to which they apply.

The inventions are distinct, each from the other because of the following reasons:

Inventions **I and II** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to substituted isoquinolines and their medicinal applications, and the second invention being directed to cinnolines and their medicinal applications.

Inventions **I and III** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to substituted isoquinolines and their medicinal applications, and the second invention being directed to indoles and their medicinal applications.

Inventions **I and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the

instant case the inventions have different functions, the first invention being directed to substituted isoquinolines and their medicinal applications, and the second invention being directed to indazoles and their medicinal applications.

Inventions **II and III** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to substituted cinnolines and their medicinal applications, and the second invention being directed to indoles and their medicinal applications.

Inventions **II and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to substituted cinnolines and their medicinal applications, and the second invention being directed to indazoles and their medicinal applications.

Inventions **III and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to substituted indoles and their medicinal applications, and the second invention being directed to indazoles and their medicinal applications.

Because these inventions are distinct for the reasons given above and 1) have acquired a separate status in the art as shown by their divergent classification, 2) have acquired a separate status in the art because of their recognized divergent subject matter, and 3) the search required for each of Groups **I, II, III or IV** are not required for any one of the other Groups, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Gabryleda Ferrari-Deleo on May 13, 2004 a provisional election was made without traverse to prosecute the invention of Group **III**, claims **77-93** and linking claims **1 and 94-97** to the degree applicable. Affirmation of this election

must be made by applicant in responding to this Office action. Claims **2-76** and, claims **1 and 94-97** to the degree not applicable, are withdrawn from further consideration by the Examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. §1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor if at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(h).

Claims **77-93**, and claims **1 and 94-97** to the degree applicable, remain under examination in the case.

The disclosure is objected to because of the following informalities:

The definitions of variables X_1 to X_4 are technically erroneous and incomplete because these definitions fails to include the proviso that
-- provided that when X_4 is a bond, one of X_1, X_2 or X_3 must be NR_3 --.

Appropriate correction is required.

Claims **1 and 77-93** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed exemplifications.

The definitions of substituents in claim **1 and 77-93** is directed to a vast number of chemical compounds which have not been described in the instant disclosure in a manner permitting the ordinary practitioner to have the guidance necessary to make a very large proportion of the compounds encompassed. Examiner finds more than 72 compounds provided in the "Examples" section at pages 171-195 (see also chemical names listed in claims

80, 84, 86 and 93), and also finds that none of these compounds discloses a structure with the multiple layers of substituents on top of substituents provided for by the noted claims. See in particular the laundry lists of substituents at lines 18-28 and 29-35 in claim **1** and repeated in part in dependent claims in less extensive lists.

Claims **95-97** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claim **95** is directed to an indeterminate set of disease conditions defined only by the VR1 receptor. Claims **96-97** are more narrowly directed to treating bladder overactivity and to treating urinary incontinence, respectively.

B. The nature of the invention is directed to administration of the indazole derivatives derivatives defined by claim **1** which are alleged to have VR1 receptor inhibitor activity.

C. The state of the prior art is incompletely defined but has disclosed that certain substituted indazoles with side chains at the 5- or 8-positions are capable of effectively interacting with the VR1 receptor as inhibitors (e.g. see PTO-892 ref. **N** at p. 3, lines 39-41; the reported activity is presumed to be the result of VR1 receptor inhibition even though this particular receptor is not mentioned in the cited reference).

D. The level of one or ordinary skill requires knowledge of how to make substituted indazoles and how to administer same to achieve an effect wherein the VR-1 receptor is inhibited. These skills are disclosed in PTO-892 ref. **N**.

E. The level of predictability in the art is moderately defined as revealed by the overlap of the structural definitions and medicinal disclosures in PTO-892 ref. **N** and in other references cited in art rejections below.

F. The amount of direction provided by the inventor is substantial in the area of how to make the instant claimed substituted indazoles, but at pages 28 and 30, respectively, the disclosure is only generic with regard to both *in vitro* and *in vivo* pharmaceutical activity; i.e. no specific pharmaceutical activity has been provided for any one of the substituted indazoles compounds the preparation of which has been disclosed herein.

G. The existence of working examples is limited to how to make the instant claimed substituted indazoles.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive in the area of medicinal administrations of the claimed substituted indazoles because of the complete lack of guidance in the form of test data. Applicant is referred to MPEP §2107.03 and the following precedent cited therein: *Ex parte Balzarini,* 21 USPQ 2d 1892 (Bd Pat App & Inter, 1992) includes guidance regarding the enhanced enablement needed to support claims directed to methods of medicinal treatment.

Claim **95** is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claim **95** has not met the written description standard of *Regents of the University of California v. Eli Lilly* (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)) which MPEP §2163 at page 2100-162, column 1, quotes as follows: "A definition by function alone 'does not suffice' to describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is.'" The instant noted claim relies on generic functional terminology exemplified by the term "disorder ... ameliorated by inhibiting [a] ... (VR1) receptor" wherein the disclosure definition thereof does not overcome the functionality of the noted term.

Claim **1** is objected to because of the following informalities:

In claim **1** at line 4, the term "or a single bond" is grammatically incomplete. Examiner suggests the term should read -- or **is** a single bond --.

Appropriate correction is required.

Claims **1, 77, 79, 80, 81, 85, 89, 92 and 94-97** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **1** the definition of subscript variable "m" as "0" is directed to peroxide compounds and is therefore unlikely to be properly part of the instant invention due to chemical instability of peroxides generally and the likelihood of interference with pharmaceutical activity when this functional group is present. Examiner suggests limitation of "m" to integers of 1-6.

In claim **79** at line 10, the terms "1-azepanyl" and "1-azocanyl" do not appear to conform to the IUPAC rules of naming heterocycles; see IUPAC Rules in the CRC Handbook of Chemistry and Physics, 60th Edition, page C-33. Inspection of the disclosure reveals multiple repetitions of said terms but fails to reveal any specific definitions of said terms. Clarification of the intended meanings of said terms is respectfully requested. See also claims **80** (lines 8-9, 14-15, 28-29, 35, 46 and 50)**, 85** (line 11)**, 89** (lines 10-11) **and 92** (lines 11-12) wherein the same terms appear without definition.

In claim **79** at line 8, the listing of "1, 2 or 3 substituents ... consisting of hydrogen ..." is technically incorrect because the listed substituents are -- alternative substituents -- and "hydrogen" is not properly part of the list because hydrogen is assumed or specified; see claim **79** at line 8 wherein the group being substituted is defined as "phenyl," aka $C_6\underline{H}_5$- (emphasis added). Examiner recommends that the noted term be amended to read as follows: -- 1, 2 or 3 alternative substituents ... consisting of hydrogen ... --. See also claim **81** at line 8, claim **85** at line 9, claim **89** at lines 8-9 and claim **92** at lines 9-10 where the identical or closely analogous errors are found.

In claims **94-97**, each claim is incomplete because the term "compound of formula (I)" has not been defined in any one of said claims or by dependence from another claim wherein said formula has been defined. Additionally, applicant is respectfully requested to limit the scope of the claimed subject matter to the subject matter elected in the noted claims and in claim **1**.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

(e) the invention was described in

(1) an application for patent described under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application filed under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a)."

Claims **1 and 77-97** are rejected under 35 U.S.C. §102(**a**) as being anticipated by **Sumitomo Pharm. Co. '255** (PTO-892 ref. **N**). (Note that this subject matter was published in Japanese in December, 2002 as WO2002/100833; see item "(87)" on the cover page of the noted reference).

Applicant is referred to page 3, lines 39-41 and to pages 213-215 wherein the definition of formula (2) in claims ***1, 2 and 24-28*** define same and its administration to treating urinary incontinence in a manner which anticipates the instant claimed subject matter.

Claims **1 and 77 and 94** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Kirchner '819** (PTO-892 ref. **C**).

Applicant is referred to the product of Examples 1 at columns 4-5 and solutions containing same which anticipates the noted claims.

Claims **1 and 77** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Biller et al. '246** (PTO-1449 ref. **J**).

Applicant is referred to claim ***10*** at columns 433 (second structure), 444 (third structure) and 459 (second structure) which are indazoles which anticipate the instant claimed subject matter.

Claims **1, 77 and 94-97** are rejected under 35 U.S.C. §102(**e**) as being anticipated by **SmithKline Beecham '809** (PTO-892 ref. **L**).

Applicant is referred to structure (IA) at page 4, to the definitions of " P and P' " at page 4, line 6, the term "indazolyl" at page 12, line 10 and the term "urinary incontinence" at page 15 at line 29 which when taken together to with the numerous references to the "VR1 receptor" (e.g. see page 15, line 16) anticipate the subject matter of the instant noted claims.

Claims **1 and 77** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Lichtenthaler et al.** (PTO-892 ref. **R**).

Applicant is referred to page 4398, last line, the compounds numbered "**27**" and "**28**," which compounds anticipate the instant noted claims.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX

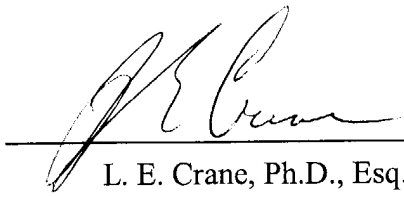
(unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
07/13/2004



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